

*C14
canceled*

- (c) greater than 3% (w/w) of a humectant to trap water in a film;
- (d) water in an amount sufficient to hydrate the nail and thereby to increase permeability of the nail in combination with said keratolytic agent;
- (e) a polymeric film forming agent; and
- (f) a volatile solvent; said film forming agent being selected so as to form a sustained release film upon application of said composition on a nail of said subject and evaporation of said volatile solvent, said sustained release film configured to trap water from said composition and maintain it in contact with said nail, said water and said humectant in combination facilitating penetration of said antifungal agent into the nail, and thereby enhancing effectiveness of said antifungal agent.

99. (New) The method of claim 93 said formulation being suitable for application by spraying.

REMARKS

This submission is in response to the final Official Action dated June 17, 2002. Claims 1-46 and 94 have been canceled, without prejudice. Claims 47, 51, 55, 59, 62, 65, 68, 70, 76, 82, 85, 93, and 96 have been amended. Claims 98 and 99 have been added. Therefore, claims 47-93 and 95-99 are pending.

Reconsideration of the above identified application, in view of the above amendments and the following remarks, is respectfully requested.

Summary of the Interview

Applicants appreciate the Examiner's time and consideration during a telephone interview between Examiner Howard, Adda Gogoris, and the undersigned held November 22, 2002 in which we discussed the foregoing claim amendments and the references cited against the claims in the final office action. We agreed to cancel claims 1-46 and 94. We agreed to amend claims 47 and 96. We further agreed to amend other claims, e.g. claim 82, to correct formal or obvious errors, such as antecedent basis. While no specific support was discussed in the telephone interview, Examiner Howard stated that the amended claims, as discussed, presented no issue of new matter. Claims 98 and 99 were not discussed.

Summary of the Arguments

Applicants respectfully submit that the claims are not obvious over the cited references, Bohn and Friedman. Specifically, (1) neither reference has a specific teaching of the 3 necessary ingredients and functional amounts as present in combination in the claimed nail varnish compositions; and (2) it would be counterintuitive to use a humectant and water on a nail with a fungal infection because water, and more generally moisture, promotes fungal growth, hence the

claimed invention is not obvious.

Support for the Present Amendments

As agreed upon during the telephone interview, the following amendments have been made to Claim 47:

Amendment	Support in the specification
" (a) <u>an antifungal effective amount of an antifungal agent</u> "	p.19, line 11-12: "lower concentrations of antifungal agent will be adequate in order to diffuse through the nail and provide the desired pharmacological action." p.20, lines 5-7: "preferably the concentration of the antifungal agents in the varnish solution is less than about 1% (w/w) and most preferably 0.3-0.9% (w/w)"
"(b) <u>a keratolytic agent in an amount sufficient to increase permeability of the nail</u> "	p.20, lines 11-12: "the keratolytic agents are added to the present invention in order to increase the permeability of and penetration into the nail:
(c) <u>greater than 3% (w/w) of a humectant to trap water;</u>	p.22, lines 15-17: "Preferably the concentration of the humectant in the varnish solution is in the range from about 3% to about 15% (w/w), and most preferably 4-10% (w/w). p.22, line 18-p.23, line 1: "Preferably the concentration of the humectant based on the weight of the non-volatile components is in the range from about 5% to about 35% (w/w), and most preferably 10-30% (w/w).
(d) <u>water in an amount sufficient to hydrate the nail and thereby to increase permeability of the nail in combination with said keratolytic agent;</u>	p.22, lines 12-14: "The presence of water in the film hydrates the nail so that the active agents can be delivered into the deeper layers of the nail."

<p><u>(e) a polymeric film forming agent selected to form a sustained release film upon application of said composition on a nail and evaporation of said volatile solvent; and</u></p>	<p>p.23, lines 12-13: "The delayed release polymeric film-forming agents, are preferably hydrophobic (water insoluble) polymers."</p> <p>p.24, lines 5-8: "The polymers provide a uniform film, retard the release rate of the drugs (agents), and can be mixed in regulated amounts to attain the desired drug release characteristics."</p> <p>p.24, lines 10-12: "Preferably the concentration of the polymeric film-forming agent based on the total weight of the non-volatile components is in the range..."</p>
<p><u>"said sustained release film configured to trap water"</u></p>	<p>p.18, lines 17-18: "Because the amount of water in the nail is very low, it is essential to achieve relatively high concentrations of water in the film."</p> <p>p.19, lines 3-6: "The presence of water in the film is of significant importance because it maintains the active agents in a saturated-reservoir solution, thus enabling the solubilized agents to be released in a controlled manner into the nail."</p>
<p><u>"said water and said humectant in combination facilitating penetration of said antifungal agent into the nail, and thereby enhancing therapeutic effectiveness of said antifungal agent"</u></p>	<p>p.19, lines 9-11: "The water entrapped in the film by the glycerol [humectant] hydrates the nail and enables low concentrations of the keratolytic to be used in order to increase the permeability of the nail."</p>

These amendments were added to further clarify the claimed properties of the nail varnish. Support for these amendments can be found in the present specification as indicated above.

Claim 96 has been amended in parallel fashion to claim 47, but is

further amended to remove the phrase "or spray" (an obvious error) as well as to the insert the following:

Amendment	Support in the specification
"film coating releasing the antifungal and keratolytic agents in <u>the respective effective amounts</u> "	p.24, lines 6-8:"the polymers provide a uniform film, retard the release rate of the drugs (agents), and can be mixed in regulated amounts to attain the desired drug release characteristic"
" <u>said water increasing permeability of the nail surface</u> "	p. 19, lines 9-10:"the water entrapped in the film by the glycerol hydrates the nail and enables.....to increase the permeability of the nail"
"facilitating penetration of the released antifungal agent <u>below</u> the nail surface"	p.22, lines13:"so that the active agents can be delivered into the deeper layers of the nail"

As represented in the telephone interview, claim 98 has been added to be directed to a method for using the formulation of claim 47 to treat fungal infection. Support for this claim can be found in the present specification as pointed out above in the schedule for claim 47 and in claim 47 itself. Support for the method of use can be found throughout the specification, including, for example, at page 17, lines 18-19, which states "for treating the nail and surrounding tissues." In addition, at page 18, lines 10-12 states,

The delivery system is in the form of a solution or spray for self-application by the patient. After application of the solution to the nail surface, the solvent evaporates and a film/coating is formed on the surface.

As agreed upon during the telephone interview, claim 82 has been amended to recite "further comprising a plasticizer." The amendment was made to correct for antecedent basis and to account for the redundancy of "comprising" language. "Comprising at least one ... plasticizers" is understood to mean the same as "comprising a plasticizer" because of the open-ended meaning of "comprising." MPEP 211.03. Support for this amendment can be found on page 25, lines 10-15.

Additional Amendments Not Discussed During the Interview

In addition to the amendments discussed, claims 51, 55, 59, 62, 65, 68, 70, 76, and 85 have been amended to recite "said composition excluding said volatile solvent." These non-narrowing amendments were made to make clear that the percentage weight basis is taken after evaporation of the solvent. Support for this amendment can be found throughout the present specification. For example, on page 18, lines 11-12 state, "[a]fter application of the solution to the nail surface, the solvent evaporates and a film/coating is formed on the surface." Then, for example, page 20, lines 8-10 read, "[p]referably the concentration of the antifungal agents based on the weight of the non-volatile components is" It is understood that since the volatile solvent evaporates, the percentage weight basis of the remaining agents is based upon the remaining "non-volatile" components of the composition.

Claim 93 has also been amended to remove "or spray" from the description of the varnish formulation. Regardless of whether the formulation is in spray form, the formulation is still a varnish. Support for this amendment can be found on page 17, lines 17-19. The spray form has been claimed in new claim 99. For support, please see original claim 93 and specification p.18, lines 10-12. Claim 93 has also been amended to remove "for treating the nail and surrounding tissues" since the claim is a composition claim, and the inclusion of such terms is not needed. Water has also been added to describe the solution. Support for this amendment can be found on page 22, lines 10-12. Also, "comprising one or more volatile solvents" has been amended to "comprising a volatile solvent" since "comprising a" means "containing one or more." MPEP 211.03. In addition, "and excipients" has been omitted from the subsection (c) again due to the "comprising" language of the claim, and because the excipients are not necessary ingredients in the composition. Lastly, "sustained release" has been added to describe the film. Support for this amendment can be found on page 18, lines 17-18 and on page 19, lines 3-6.

No new matter is added by these amendments.

The Art Rejection

Claims 1-97 were rejected under 35 U.S.C. §103 as obvious over Bohn (U.S. Patent No. 5,264,206) in view of Friedman (U.S. Patent No.

5,160,737) for reasons of record. Briefly, the Examiner contended that Bohn teaches, at various locations throughout the reference, a nail lacquer composition for treating mycosis of the nails, comprising antifungal agents, volatile solvents, additives which have humectant properties, water, film forming agents, and keratolytic agents. The Examiner acknowledged that Bohn does not teach a sustained release therapeutic nail varnish composition, but relied on Friedman to disclose the sustained-release of pharmacological active agents which are known in the art for treating dermatological conditions "of the skin." The Examiner concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a sustained release composition taught by Friedman which is known in the art for treating conditions "of the skin," in a nail varnish composition taught by Bohn et al.

This rejection is traversed, and reconsideration is respectfully requested.

In response to the Examiner's rejection, applicants respectfully submit that Bohn has no specific teaching of the combination of the three presently claimed necessary ingredients: an antifungal, a keratolytic, and a humectant, nor of how they cooperate in the present invention in an advantageous manner to trap water and maintain it close to the nail and thereby increase the nail permeability which is also enhanced by the keratolytic agent. The result is that the nail plate and/or nail matrix and/or nail bed becomes more accessible to the antifungal agent, which increases the

effectiveness of the antifungal agent. Rather, Bohn discloses ingredients in the form of "laundry lists" without specific direction and without specific teaching or motivation to arrive at the presently claimed invention. For example, as discussed in the telephone interview, Bohn states that various optional ingredients can be added to antifungal nail varnish compositions such as perfumes or keratolytics. At col. 5, lines 9-20 (emphasis not original), Bohn states:

The nail lacquers according to the invention can also contain additives common in cosmetics, such as plasticizers based on phthalates or camphor, colorants or pigments, perlescent agents, sedimentation retardants, sulfonamide resins, silicates, perfumes, wetting agents such as sodium dioctylsulfosuccinate, lanolin derivatives, sunscreen agents such as 2-hydroxy-4- methoxybenzophenone, substances having antibacterial activity, and substances with a keratolytic and/or keratoplastic action, such as ammonium sulfite, esters and salts of thioglycolic acid, urea, allantoin, enzymes and salicylic acid.

Thus, Bohn treats keratolytics as optional ingredients, on a par with colorants and perfumes and without a hint of a suggestion that they would increase the effectiveness of the composition. Similarly, lanolin derivatives, urea and allantoin, which the Examiner takes to be humectants (although there is no recitation of that function nor mention of any particular effective amount for these substances), are also considered optional and on a par with colorants and perfumes. Bohn also optionally uses water in its formulations. In Examples 7-9, Bohn discloses various embodiments of the invention (col. 6, lines 45-68). Example 7 discloses an antimycotic and solvent,

but no water; whereas Example 8 discloses a solvent, antimycotic, and water. See Bohn, Col. 6, lines 52-61. Both examples represent acceptable formulations under the invention, and clearly demonstrate that water is not a required component. Again, there is no hint that water could contribute to the effectiveness of the antifungal formulation.

Thus, in Bohn, keratolytics, humectants and water are not singled out for combined use, but are treated on a par with such other optional ingredients as coloring, perfumes and sedimentation retardants which have no positive bearing on the antifungal effectiveness of the Bohn compositions. Nor does Bohn contain any suggestion (explicit or implicit) why the particular combination of claimed ingredients should be used together. For example, the Bohn Examples (at col. 6, lines 45-68) recite isopropyl alcohol, ethyl acetate, and an antimycotic; only 2 examples recite water. Nor does Bohn spell out the functions and effective amounts of particular optional ingredients. The secondary reference, Friedman, does not supply the disclosure or the motivation lacking in Bohn.

Table 1 below depicts which ingredients are necessary, not necessary, and not discussed in the claimed invention, and in the Bohn and Friedman references. The antifungal, keratolytic, humectant, water, and sustained release components all cooperate in the present invention. However, Bohn requires only the antifungal, and Friedman requires only the sustained release component. Neither reference requires

that a humectant (in sufficient quantity to attract water accordingly) or water be necessary in the formulations disclosed.

Table 1

Ingredients	Present Invention	Bohn Reference	Friedman Reference
Antifungal (antimycotic)	Necessary	Necessary	Not necessary (can be antifungal, antibiotic, antiseptic, antiviral, or other agent)
Keratolytic	Necessary	Not necessary	Not necessary
Humectant	Necessary	Not necessary	Not necessary
Water	Necessary	Not necessary	Not necessary
Film forming agent forming a sustained release film	Necessary	Not disclosed (no sustained release film)	Necessary but <u>not</u> for a nail varnish

As indicated by Table 1, Friedman requires a film forming agent for a sustained release film, but does not require any other ingredients nor does it mention a nail varnish in particular. As done in Bohn, Friedman also provides, at different places in the reference, laundry lists of optional ingredients which may be combined with the sustained release film. However, Friedman fails to mention a fungal nail varnish. Rather, Friedman discloses sustained release in dental or dermatological agents such as mouthwash, toothpaste/gel, moisturizers, or retinoid A. See, e.g., col.

22, lines 2-7 and col.21, lines 55-58. Friedman does not provide a teaching or motivation to use a sustained release film in a fungal nail varnish. As applicants explain below, fungal nail infections are not the same as fungal infections of the skin, but are persistent and much more difficult to treat.

In addition, Friedman does not provide any motivation to specifically combine an antifungal, keratolytic, and a humectant (and water). At best, Friedman includes an antifungal as one of many pharmacological agents in a laundry list (col. 11, lines 44-50). With respect to the keratolytic, Friedman does not disclose any ingredient as a keratolytic *per se*, but includes reference to substances which in appropriate quantities, not disclosed by Friedman, may function as keratolytics. For example, in col. 14, line 6, Friedman states,

"Examples of suitable antiviral agents which may be employed in accordance with the present invention include acyclovir, idoxuridine, salicylic acid and its derivatives, amantadine, ribavirin, interferons, etc."

Friedman teaches salicylic acid as an antiviral agent, but the Examiner takes it to be a keratolytic. Since no amount is mentioned, Friedman does not disclose or suggest a keratolytic effective amount. Moreover, the salicylic acid is referred to as one of many in the list, not required in any particular composition, and on par with other antiviral agents, the majority of which would not cooperate to enhance the antifungal effects of any composition, let alone a nail varnish composition which Friedman does not disclose.

Friedman also fails to require the presence of a humectant in any of its compositions. Specifically, Friedman states

"the compositions may contain demulcents/humectants (i.e., plasticizers) such as polyethylene glycol 400-to-4000, glycerol, sorbitol, or mineral oil in concentrations of about 1% by weight."

Col. 16, lines 18-21. Furthermore, Friedman uses concentrations at about 1%. Therefore, not only does Friedman not require the humectant, the concentrations, when used, are not in the effective amount required by the present invention. By contrast, the present specification states (p.23, lines 2-6):

at lower concentrations (less than 2% w/w based on the total weight of the composition) as a plasticizer, at this lower concentration range [the humectant] is not efficient as a humectant and therefore higher concentrations (above 3% w/w) ... are required in order to be effective as a humectant.

Therefore, Friedman fails to provide the necessary motivation or teaching for any of the 3 required ingredients of the present invention.

The inclusion of a humectant and water together with an antifungal and keratolytic agent for treating fungal nails is counter-intuitive given the nature of the growth of nail fungus. The humectant agent is required in a quantity sufficient (at least 3%) for the retention of sufficient water within the sustained release film to "soften" the nail. However, the presence of water or moisture is associated with promoting nail fungal growth. See Exhibit A (attached hereto), from the American

College of Foot and Ankle Surgeons, which discusses fungal infection and fungal growth. Specifically, the reference discusses how moist surroundings make feet susceptible to fungal infection (see Exhibit A, page 2). Therefore, when nail fungus is present, it is recommended as a preventive measure that the affected areas be kept dry (See MSN Medical Encyclopedia website information, Exhibit B, page 1; Medline plus Medical Encyclopedia website information, Exhibit C, page 2). The conventional wisdom in the art was thus that water is undesirable because water promotes fungal growth. Hence, it is not obvious to use water and substances that trap water (sustained release film, humectant) and keep them close to the infected nail.

In the presently claimed invention, the water in the humectant creates a moist environment -- the very thing that should be avoided. The inventors have discovered that the presence of water is beneficial to create an environment where the antifungal can be absorbed properly to treat the fungus deeper than the nail surface, all against the conventional wisdom in the art. Therefore, applicants respectfully submit that the claimed invention is not obvious over Bohn in view of Friedman, and the present rejection should be withdrawn.

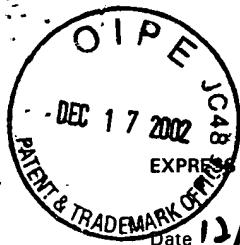
In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

Sandra Lee
Sandra S. Lee
Reg. No. 51,932
Attorney for Applicants

DARBY & DARBY, P.C.
Post Office Box 5257
New York, NY 10150-5257
Phone (212) 527-7700



EXPRESS MAIL CERTIFICATE

Date 12/17/02

Label No. EY 251497075 US

I hereby certify that, on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to the Assistant Commissioner for Patents, Washington, DC 20231 by "Express Mail Post Office to Addressee" service.

L. Douglas
Name (Print)

L. R. D.
Signature

Customer No.:



07278

PATENT TRADEMARK OFFICE

Docket No: 3940/OK188

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Michael Friedman et al.

Serial No.: 09/534,960

Art Unit: 1615

Confirmation No.: 3862

Filed: March 27, 2000

Examiner: S. Lee Howard

For: CONTROLLED DELIVERY SYSTEM OF ANTIFUNGAL AND KERATOLYTIC AGENTS FOR LOCAL TREATMENT OF FUNGAL INFECTIONS OF THE NAIL AND SURROUNDING TISSUES

Mark-up Accompanying Final Amendment
Under 37 C.F.R. §1.121

47. (Amended) A sustained release therapeutic nail varnish composition comprising:

- (a) an antifungal effective amount of an antifungal agent;
- (b) a keratolytic agent in an amount sufficient to increase permeability of the nail;

- (c) greater than 3% (w/w) of a humectant to trap water;
- (d) water in an amount sufficient to hydrate the nail and thereby to increase permeability of the nail in combination with said keratolytic agent;
- (e) a polymeric film forming agent selected to form a sustained release film upon application of said composition on a nail and evaporation of said volatile solvent; and
- (f) a volatile solvent;

[said film forming agent being selected so as to form a film upon application of said composition on a nail and evaporation of said volatile solvent,] said sustained release film configured to trap water from said composition and maintain it in contact with said nail, said water and said humectant in combination facilitating penetration of said antifungal agent into the nail, and thereby enhancing therapeutic effectiveness of said antifungal agent.

51. (Amended) The nail varnish of claim 47, wherein said antifungal agent is present in an amount of less than about 5% of the total weight of the [non-volatile components] composition excluding said volatile solvent.

55. (Amended) The nail varnish of claim 47, wherein said keratolytic

agent is present in an amount of from about 0.05% to about 5% of the total weight of the [non-volatile components] composition excluding said volatile solvent.

59. (Amended) The nail varnish of claim 56, wherein said antibacterial agent is present in an amount of from about 0.05% to about 5% of the total weight of the [non-volatile components] composition excluding said volatile solvent.

62. (Amended) The nail varnish of claim 56, wherein said antiviral agent is present in an amount of from about 0.8% to about 8% of the total weight of the [non-volatile components] composition excluding said volatile solvent.

65. (Amended) The nail varnish of claim 56, wherein said antipsoriatic agent is present in an amount of from about 0.1% to about 10% of the total weight of the [non-volatile components] composition excluding said volatile solvent.

68. (Amended) The nail varnish of claim 47, wherein said humectant is present in an amount of from about 5% to about 35% of the total weight of the [non-volatile components] composition excluding said volatile solvent.

70. (Amended) The nail varnish of claim 47. wherein said water is

present in an amount of from about 0.4% to about 25% of the total weight of the [non-volatile components] composition excluding said volatile solvent.

76. (Amended) The nail varnish of claim 47, wherein said polymeric film forming agent is present in an amount of from about 8% to about 35% total weight of the [non-volatile components] composition excluding said volatile solvent.

82. (Amended) The nail varnish of claim 47, further comprising [wherein said at least one additional excipient is selected from the group consisting of] a plasticizer[s].

85. (Amended) The nail varnish of claim 82. wherein said plasticizer is present in an amount of from about 0.5% to about 10% of the total weight of the [non-volatile components] composition excluding said volatile solvent.

93. (Amended) A method of preparing a sustained release therapeutic varnish [or spray] formulation [for treating the nail and surrounding tissues], comprising the steps of:

(a) preparing a solution comprising water and [one or more] a volatile solvent[s];

- (b) adding water to the solution prepared in (a);
- (c) dissolving a keratolytic agent[,] and an antifungal agent [and excipients] into the solution prepared in (b);
- (d) adding an humectant to the solution prepared in (c); and
- (e) dissolving a polymeric film forming agent in the solution prepared in (d);

said film forming agent being selected so as to form a sustained release film upon application of the formulation on a nail and evaporation of said volatile solvent, said sustained release film configured to trap water in contact with the nail and the surrounding tissues.

96. (Amended) A sustained release therapeutic nail varnish composition comprising:

- (a) an antifungal effective amount of an antifungal agent;
- (b) a keratolytic agent in an amount sufficient to increase permeability of the nail;
- (c) a humectant to trap water;
- (d) a polymeric film forming agent;
- (e) water; and
- (f) a volatile solvent; wherein upon application on a nail, the volatile

solvent evaporates and a sustained release film coating forms on the surface of the nail, the sustained release film coating releasing the antifungal and keratolytic agents in [therapeutic levels] respective effective amounts over a prolonged period of time and trapping water in contact with the nail; the humectant retaining [the] water in the film; and said keratolytic agent and said water increasing permeability of the nail surface and facilitating penetration of the released antifungal agent [beyond] below the nail surface.